UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

MITSUBISHI TANABE PHARMA CORPORATION, JANSSEN PHARMACEUTICALS, INC., JANSSEN PHARMACEUTICA NV, JANSSEN RESEARCH AND DEVELOPMENT, LLC, and CILAG GMBH INTERNATIONAL, Plaintiffs, v. SANDOZ INC., *et al.*, Defendants.	Civil Action No. 17-5319 (FLW)(DEA) (consolidated) **FILED UNDER SEAL** ***Document Filed Electronically***

DEFENDANT ZYDUS PHARMACEUTICALS (USA) INC.'S TRIAL BRIEF

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Defendant Zydus Pharmaceuticals (USA) Inc. ("Zydus") respectfully submits this pretrial brief to preview the legal and factual issues to be tried.

I. INTRODUCTION

This case is about the validity of the Patents-in-Suit (defined below), all of which relate to a chemical compound known as canagliflozin. Canagliflozin is in a class of compounds known as sodium-glucose cotransporter ("SGLT") inhibitors. As scientists have known for decades, SGLT inhibitors inhibit the reabsorption of glucose in the kidneys, which facilitates the excretion of glucose in urine, which in turn lowers glucose levels in the blood—an important factor in the management of diabetes.

Zydus is a generic pharmaceutical company. Zydus has sought approval from the Federal Drug Administration ("FDA") to manufacture and market generic versions of Invokana® (canagliflozin) and Invokamet® (canagliflozin and metformin) (the "Invokana Products"), which are indicated for the treatment of type 2 diabetes, along with diet and exercise. Founded in 2005, Zydus is located in Pennington, New Jersey. Zydus manufactures and sells over 100 generic pharmaceutical products with the FDA's approval. Like other generic pharmaceutical companies, Zydus provides the U.S. market with generic pharmaceutical products at lower prices than the corresponding brand-name pharmaceutical products.

Plaintiffs Mitsubishi Tanabe Pharma Corporation ("Mitsubishi"), Janssen Pharmaceuticals Inc., Janssen Pharmaceutica NV (together, "Janssen"), and Cilag GmbH International ("Cilag," collectively "Plaintiffs") are brand-name pharmaceutical companies. Mitsubishi is the assignee of the Patents-in-Suit. As is common, Mitsubishi's medicinal chemists are listed as the inventors of the original Patents-in-Suit and assigned them to their employer. Janssen and Cilag are the exclusive licensees of the Patents-in-Suit. Janssen markets and sells the Invokana Products in the United States.

In this action, Plaintiffs seek a declaration that, if Zydus commercially manufacturers, uses, offers for sale, or sells its proposed generic versions of the Invokana Products within the United States, Zydus would infringe the Patents-in-Suit. Zydus' concedes that doing so would infringe the Patents-in-Suit—if the Patents-in-Suit were valid. But they are not. As Zydus will show at trial, and previewed below, the Patents-in-Suit are invalid because canagliflozin is an obvious derivative, in light of prior art, of earlier-patented compounds, including dapagliflozin (also an SGLT inhibitor). Dapagliflozin is the active pharmaceutical ingredient in Farxiga®, which, like the Invokana Products, is indicated for the treatment of type 2 diabetes, along with diet and exercise. In addition, as Zydus will also show at trial, and previewed below, the '788 patent is invalid for the independent and alternative reason that it violates the doctrine of obviousness-type double patenting.

II. BACKGROUND

A. The Patents-in-Suit

The Patents-in-Suit are the '788 patent (U.S. Patent No. 7,943,788), the '219 patent (U.S. Patent No. 8,222,219), and the '403 patent (U.S. Patent No. 8,785,403) (DTX-1, 2 and 3, respectively) (the "Patents-in-Suit").[1] All three patents belong to the same patent family. Each of the Patents-in-Suit are entitled "Glucopyranoside Compound." The '788 patent and '403 patent are both directed to the compound canagliflozin. The '219 patent is directed to a method of treatment of diabetes using canagliflozin. Plaintiffs contend that all three of the Patents-in-Suit are relevant to Invokamet®, while only the '788 and '219 are relevant to Invokana®.

[1] "DTX-_" refers to the enumerated trial exhibit pre-marked by Zydus and exchanged with Plaintiffs. The select DTXs referenced herein are attached to the accompanying Declaration of Hershy Stern, dated May 28, 2020.

B. The Invokana Products

Invokana® is marketed as an antidiabetic drug. Its active pharmaceutical ingredient is canagliflozin. Invokana® was approved by the FDA in March 2013. Invokana® is marketed and sold in the U.S. by Janssen. As of May 2020, the average retail price of 30 tablets of Invokana® at 300 mg is $618.92. Invokamet® is also marketed as an antidiabetic drug. Invokamet® combines canagliflozin with a second active pharmaceutical ingredient known as metformin. Invokamet® was approved by the FDA in August 2014. Invokana® and Invokamet® are both marketed and sold in the U.S. by Janssen. As of May 2020, the average retail price of 60 tablets of Invokamet® at 150/1000 mg is $618.43.[2]

C. Type 2 Diabetes Mellitus

The American Diabetes Association defines type 2 diabetes mellitus ("diabetes") as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. As a result, excess glucose accumulates in the blood, which can cause health problems, including heart disease, vision loss, and kidney disease. Approximately 30.3 million adults in the U.S. have diabetes, which is the seventh leading cause of death in the U.S. and the number one cause of kidney failure, lower-limb amputations, and adult onset of blindness. The treatment of diabetes has historically centered on increasing insulin availability (either through direct insulin administration or through agents that promote insulin secretion) and/or improving sensitivity to insulin. However, standard anti-hyperglycemic agents have significant drawbacks, including hypoglycemia and weight gain. At the relevant time, there was, and remains, a strong incentive to develop novel drugs with improved efficacy and safety.

[2] Prices for the Invokana Products found at https://www.goodrx.com (last visited May 22, 2020).

D. The Evolution Of SGLT2 Inhibitors As Anti-Diabetic Agents

For over 100 years, medicinal chemists have known that phlorizin, a naturally occurring compound, lowers blood glucose levels. In the 1930s, researchers discovered why: phlorizin inhibits the function of compounds known as sodium-glucose co-transporters (defined above as "SGLTs").[3] Kidneys filter the blood constantly to remove waste and excess fluid, which is excreted from the body as urine. SGLTs bind to glucose in the waste and excess fluid before it is excreted and transport it back into the bloodstream. By inhibiting the function of SGLTs (*i.e.*, inhibiting the transport of glucose back into the bloodstream), phlorizin causes the human body to excrete more glucose in urine.

Despite phlorizin's known ability to reduce blood glucose, phlorizin—unmodified—was unsuitable as an anti-diabetic agent. Among other reasons, phlorizin breaks down easily in the body when taken orally (*i.e.*, metabolized), which prevents phlorizin from reaching a therapeutic dose in the bloodstream. Nevertheless, because the underlying biological mechanism of phlorizon was promising, and because there is an enduring need for alternative therapeutic agents for the treatment of diabetes, the race was on to find a metabolically-stable SGLT inhibitor.

In 1997, following in the footsteps of many, Mitsubishi's predecessor (Tanabe Seiyaku) developed an SGLT inhibitor known as T-1095A for potential use in the treatment of diabetes. Despite initial clinical trials, T-1095A was never fully developed. Like phlorizin, T-1095A is rapidly metabolized, rendering it, for practical purposes, pharmaceutically ineffective, at least when administered orally. Thus, by the late 1990s, the relevant medicinal chemistry community—including Mitsubishi's predecessor—was actively searching for an SGLT inhibitor

[3] Both SGLT-1 and SGLT-2 inhibitors will factor into the testimony at trial. For the purposes of this brief, suffice it to say that dapagliflozin and canagliflozin are both SGLT-2 inhibitors.

that was, not only effective at inducing glucose excretion, but also, unlike phlorizin and T-1095A, less prone to rapid metabolism when administered orally.

In the early 2000s, non-party Bristol Myers Squibb Co. ("BMS") disclosed a solution to this problem (*i.e.*, the rapid metabolization of then-known SGLT inhibitors). The key innovation was swapping out an oxygen bond (which breaks down easily during digestion) for a carbon bond (which does not). SGLT inhibitors with an oxygen bond (such as phlorizon and T-1095A) are known as "O-glucosides." The "O" stands for oxygen. SGLT inhibitors with a carbon bond (such as dapagliflozin and canagliflozin) are known as a "C-glucosides." The "C" stands for carbon. As a result of this innovation, the SGLT2 inhibitor patented and disclosed by BMS—which came to be known as dapagliflozin—could be administered orally without rapid metabolization and, therefore, reach a therapeutic dose in the bloodstream.

On July 2, 2002, the '126 patent (U.S. Patent No. 6,414,126) was issued and assigned to BMS. The '126 patent disclosed several C-glucosides, one of which was dapagliflozin and another of which was labelled Example 10. The '126 patent taught how to synthesize those compounds and also how to test their efficacy as SGLT inhibitors in what is known as an assay, both of which a person of ordinary skill in the art could easily replicate.

On February 4, 2003, the '117 patent (U.S. Patent No. 6,515,117) was issued and assigned to BMS. The '117 patent related exclusively to one of the C-glucosides previously disclosed in the '126 patent. That compound was dapagliflozin. By singling out dapagliflozin as the only compound in the '117 patent, BMS telegraphed to the relevant medicinal chemistry community that it was the single most promising SGLT2 inhibitor among the C-glucosides disclosed in the '126 patent. Significantly, the '117 patent also disclosed how to synthesize dapagliflozin in multi-kilogram batches—a not-so-subtle clue to any medicinal chemist paying

attention. That is because an active pharmaceutical ingredient typically is synthesized by the kilogram only when it has shown sufficient promise to be used in clinical trials.

The implications were not lost on Mitsubishi's medicinal chemists.

By early 2003, having evidently scoured the patent filings of its competitors for clues, Mitsubishi's medicinal chemists began synthesizing several of the compounds described in the '126 patent. By August 2003, as reflected in Mitsubishi's contemporaneous lab notebooks, Mitsubishi chemists had successfully synthesized dapagliflozin and conducted assays on it using methods almost identical to those described in the '117 patent.[4] Mistubishi's internal documents dispel any doubt as to how Mitsubishi identified dapagliflozin as a lead compound, labelling it as "patent compound BMS US 6515117" (*i.e.*, the '117 patent).[5]

Mitsubishi chemists subsequently designed the molecule that became known as canagliflozin (*see, e.g.*, DTX-120)—the compound that Zydus contends is an obvious derivative of dapagliflozin in light of prior art.[6] Indeed, a Mitsubishi medicinal chemist, Sumihiro Nomura, later acknowledged in a presentation he prepared that canagliflozin was a modified version of a "**C-glucoside disclosed by BMS**." DTX-085 at 1 ("Metabolically more stable C-glucosides than O-glucoside, T-1095A were explored. C-glucoside disclosed by BMS was modified into bearing heteroaromatic ring") (first bullet point under "Exploration of C-Glucoside").

Having synthesized both dapagliflozin and canagliflozin, Mitsubishi began performing assays to compare their efficacy as SGLT inhibitors. As expected—given that Mitsubishi had

[4] *See* DTX-089 at 96 (synthesis of dapagliflozin); DTX-073 at 29 (effect of dapagliflozin on glucose excretion); DTX-072 at 61 (SGLT inhibition assay on dapagliflozin).

[5] *See* DTX-088 at 11776; DTX-122 (certified translation of DTX-088).

[6] The parties dispute the so-called conception date (*i.e.*, the earliest possible priority date), which is the subject of one of Zydus' two motions *in limine*. *See* D.I. Nos. 136, 150, 153, and 154.

employed a "bioisosteric replacement" strategy to design canagliflozin (*see infra* Section III.B.3.)—the results confirmed that canagliflozin and dapagliflozin have comparable biological activity. DTX-090 at 8 (comparing canagliflozin [1037284] with dapagliflozin [1031671]).

Each of the Patents-in-Suit were filed ***after*** the patents for dapagliflozin (the '126 patent and the '117 patent) had already been published and assigned to BMS on July 2, 2002 and February 4, 2003 respectively. Specifically, the applications that ultimately resulted in the issuance of the '788 patent, the '219 patent, and the '403 patent were filed on January 31, 2005, July 1, 2011, and June 12, 2012 respectively.

In 2011, BMS filed a New Drug Application ("NDA") for dapagliflozin with the FDA. BMS also sought the approval of the FDA's counterpart in Europe. In 2012, the European regulatory authority approved the use of dapagliflozin for the treatment of diabetes. BMS immediately began selling dapagliflozin throughout Europe under the trade name Farxiga®. Farxiga® thus became the first SGLT2 inhibitor to be placed into clinical practice and distributed on the global market. In January 2014, the FDA also approved dapagliflozin for the treatment of diabetes, and BMS began selling Farxiga® in the U.S.

In 2012, Janssen filed an NDA for canagliflozin with the FDA. In March 2013, the FDA approved canagliflozin for the treatment of diabetes, which is the active pharmaceutical ingredient in the Invokana Products.

III. THE PATENTS-IN-SUIT ARE INVALID FOR OBVIOUSNESS

A. The Legal Framework

Under the "framework" established by the Supreme Court in *Graham v. John Deere Co.*, 383 U.S. 1, 14 (1966) and reaffirmed in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 427 (2007) ("*KSR*"), the Court must consider the three primary factors in an obviousness inquiry:

"(i) the level of ordinary skill in the pertinent art, (ii) the scope and content of the prior art, and

(iii) the differences between the prior art and the claims at issue." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014) (quoting *KSR*, which in turn quotes *Graham*), rehearing *en banc* denied, 769 F.3d 1339 (Fed. Cir. 2014), *cert.* denied, 135 S. Ct. 2050 (2015) ("*BMS*"). These three primary factors are typically considered together and referred to as the "*prima facie* case." *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007).

The ultimate question is "whether there was an apparent reason [for a POSA] to combine the known elements [in the prior art] in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. Whether a chemist had a reason to modify particular prior art compounds "generally follows a two-part inquiry." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 923 F. Supp. 2d 602, 652 (D. Del. 2013), *aff'd*, 752 F.3d 967 (Fed. Cir. 2014) (citation omitted). "First, the court determines whether a [POSA] would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts." *Bristol-Myers Squibb*, 923 F. Supp. 2d at 652 (citations and quotations omitted). "A lead compound is a compound in the prior art that would be a natural choice for further development efforts." *BMS*, 752 F.3d at 973 (citation and quotations omitted). A showing that medicinal chemists were "*actually treating and using*" the lead compound as such in the relevant time-frame, confirms that there was a "reason to select" that compound as a lead compound. *BMS*, 752 F.3d at 974 (emphasis in original).

Second, the court determines "whether the prior art would have supplied [a POSA] with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success." *Bristol-Myers Squibb*, 923 F. Supp. 2d at 652 (citation and quotation omitted). "The motivation to modify that lead compound can come from any number

of sources and need not necessarily be explicit in the art." *BMS*, 752 F.3d at 973; *see also KSR*, 550 U.S. at 420 ("any need or problem known in the field … can provide a reason for combining the elements in the manner claimed"). "It is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old." *BMS*, 752 F.3d at 973 (citation, quotations and alterations omitted). "Where, as here, the patent at issue claims a chemical compound, the analysis … often turns on the structural similarities and differences between the claimed compound and the prior art." *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1007 (Fed. Cir. 2009) (citation and quotations omitted).

Once Zydus demonstrates a *prima facie* case of obviousness, the burden will shift to Plaintiffs to rebut that case by offering objective evidence of nonobviousness—*i.e.*, secondary considerations. KSR, 550 U.S. at 415. However, "a strong case of *prima facie* obviousness . . . cannot be overcome by a far weaker showing of objective *indicia* of nonobviousness." *Tokai Corp. v. Easton Enters., Inc.*, 632 F.3d 1358, 1371 (Fed. Cir. 2011). Indeed, where, as here, the putative invention involves "no more than 'the predictable use of prior art elements according to their established functions,' the secondary considerations are inadequate to establish nonobviousness as a matter of law." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) (quoting *KSR*, 550 U.S. at 417).

B. Zydus Will Establish A Prima Facie Case Of Obviousness

At trial, Zydus will make a prima facie case that the Patents-in-Suit are obvious because, as one of Zydus' experts, Dr. Thomas D. Bannister, Ph.D. ("Dr. Bannister"), will testify: (i) a POSA would have selected dapagliflozin as a lead compound for further development and modification, (ii) the prior art provided motivation for a POSA to the make changes to dapagliflozin to arrive at canagliflozin, and (iii) a POSA would be motivated to make the

relevant modifications to dapagliflozin with a reasonable expectation of successfully arriving at a "new" metabolically-stable SGLT2 inhibitor because, among other reasons, the substitutions Mitsubishi made to dapagliflozin are bioisosteric (defined and discussed below).

1. The Relevant POSA

With respect to the '788, '219, and '403 patents, the relevant field of art includes chemistry, chemical engineering, and pharmacology, in particular with regard to SGLT inhibitors. A POSA as of the time of the alleged invention would have been part of a team including people of multiple different skills, including those who may have an advanced degree in organic chemistry, medicinal chemistry, or a related discipline, and/or have experience preparing, formulating, characterizing, and/or analyzing pharmaceutical compounds and products for several years and would have been motivated to modify those compounds to develop proprietary drugs in the same therapeutic class. Such a POSA would have access to individuals having expertise in chemistry and pharmacology and would collaborate with them.

2. Dapagliflozin Was A "Natural Choice" For A Lead Compound

As Zydus will demonstrate at trial, a POSA would have considered dapagliflozin to be a lead compound, *i.e.*, "a compound in the prior art that would be a natural choice for further development efforts." *BMS*, 752 F.3d at 973 (citation and quotation omitted). As of July 31, 2004, due to, among other things, the limited number of then-existing active pharmaceutical ingredients used in the treatment of diabetes and their potential side-effects, there was a clear medical and commercial incentive to develop additional and alternative active pharmaceutical ingredients. The "abundance of interest in the therapeutic use of SGLT2 inhibitors for the treatment" of diabetes was amply reflected in the significant volume of published research and "patenting activity amongst several pharmaceutical companies." Handlon, A., *Sodium glucose co-transporter (SGLT2) inhibitors as potential antidiabetic agents*, 15(11) Expert Opin. Ther.

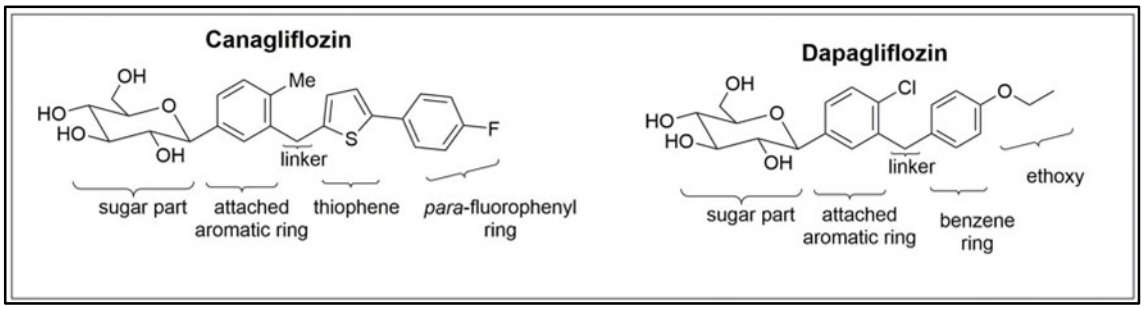
Patents 1531, 1539 (2005) (DTX-196). Indeed, Mitsubishi itself and BMS, among others, had conducted and were conducting substantial research into SGLT2 inhibitors. A POSA would, therefore, have been motivated to select SGLT2 inhibitors as a class of potential lead compounds. *Cf. BMS*, 752 F. 3d at 974 (where "carbocyclic analogs were generating a great deal of interest among researchers searching for compounds with antiviral activity, … district court had sufficient evidence to conclude that [a POSA] would have studied carbocyclic analogs 'as a promising area' for antiviral drug discovery").

Further narrowing the field of potential lead compounds, a POSA would have chosen among the SGLT2 inhibitors already known in the art. In particular, as Dr. Bannister will testify at trial, dapagliflozin was the "natural choice for further development" (*BMS*, 752 F.3d at 973) among the SGLT2 inhibitors already known in the art for multiple reasons, including that (i) prior art taught towards exploring C-glucosides to solve the metabolic stability issues inherent to O-glucosides, (ii) prior art suggested the improved efficacy of C-glucosides, (iii) BMS had singled out dapagliflozin, a C-glucoside compound in the '117 patent, suggesting that it as promising lead compound, (iv) BMS had disclosed in the '126 patent the process for synthesizing dapagliflozin in volumes ordinarily associated with clinical studies, and (v) BMS's disclosure in the '117 and the '126 patent of how to conduct an inhibition assay to study the compound's pharmacological activity, again, a something typically associated with the study of promising lead compounds. Based on the foregoing factors, dapagliflozin qualifies as a lead compound. Even standing alone, the fact that BMS was "*actually treating and using*" dapagliflozin as a lead compound confirms that a POSA had a "reason to select" it as a lead compound. *BMS*, 752 F.3d at 974 (emphasis in original).

3. A POSA Would Have Had A Motivation To Modify Dapagliflozin To Achieve A Metabolically-Stable SGLT2 Inhibitor With A Reasonable Expectation Of Success

As Zydus will demonstrate at trial, a "skilled artisan would have been motivated to combine the teachings of the prior art references to achieve [a metabolically-stable SGLT2 inhibitor], and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007) (citation and quotation omitted). "It is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old." *BMS*, 752 F.3d at 973. While "formulation science carries with it a degree of unpredictability, 'obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.'" *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) (citation omitted).

Here, the following comparison of the molecular structures of dapagliflozin and canagliflozin shows that they are structurally similar:



Translating the above chart into English (albeit the English of a POSA), dapagliflozin and canagliflozin have *only three structural differences*: (i) the 4-position substituent in Ring A is a 4-Cl in case of dapagliflozin, while it is 4-Me in case of canagliflozin; (ii) Ring B is an aromatic (phenyl) ring in dapagliflozin, while it is heteroaromatic (thiophene) in canagliflozin; and

(iii) the substituent on Ring B is an ethoxy group (on the right side, as drawn) in dapagliflozin, rather than a *para*-fluorophenyl group in canagliflozin. Dapagliflozin and canagliflozin are *otherwise structurally identical*.

As Dr. Bannister will testify at trial, and previewed below, a POSA would have been motivated to make the foregoing changes to dapagliflozin and have a reasonable expectation of successfully arriving at a "new" metabolically-stable SGLT2 inhibitor because, among other reasons, the substitutions are bioisosteric. Bioisosteres are substituents (sub-components of a molecule) with similar physical, chemical and/or biological properties. *In re Merck & Co., Inc.*, 800 F.2d 1091, 1096 (Fed. Cir. 1986) ("bioisosteric replacement" is the "substitution of one atom or group of atoms for another … [which] provides molecules having the same type of biological activity"). Conceptually, bioisosteres are analogous to synonyms in the English language—that is, near, if not exact, replacements for each other that one would expect to have the same function. Bioisosterism has been "commonly used by medicinal chemists [for decades] in an effort to design and predict drug activity." *Id.* at 1096; *see also Lima, L. et al., Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design*, 12 Curr. Med. Chem. 23–49, 48 (2005) (using bioisosteres, "we are able to predict the expected bioavailability for the new bioactive compounds designed as a drug candidate") ("Lima") (DTX-199). Thus, using a "known bioisosteric replacement … along with structural similarity, leads to a 'reasonable expectation' that the desired activity will result." *Imperial Chem. Indus., PLC v. Danbury Pharmacal, Inc.*, 777 F. Supp. 330, 370 (D. Del. 1991) (finding obviousness based on "bioisosteric replacement" and "structural similarity"), *aff'd*, 972 F.2d 1354 (Fed. Cir. 1992) ("affirmed on the basis of the court's fine opinion"); *see also BMS*, 752 F.3d at 975-76 (change was obvious where it had already been shown to have desirable properties in a similar context).

a. Substitution of the distal phenyl ring with a thiophene ring

Dapagliflozin has a distal phenyl ring. Dr. Bannister will testify that a POSA would have known that thiophene rings and phenyl rings are "classical bioisosteres." Patani, G. *et al.*, *Bioisosterism: A Rational Approach in Drug Design*, 96(8) Chem. Rev., 3147, 3158 (1996) ("Patani") (DTX-208) ("The use of the classical bioisosteres benzene, thiophene, and pyridine resulted in analogues with retention of biological activity within different series of pharmacological agents."). Therefore, a POSA would have expected that the distal phenyl ring could be replaced with a thiophene ring "with retention of biological activity." *Id*. Moreover, a 2002 MDL Drug Data Report survey found that substitution of 2-thiophene for phenyl was the second-most common ring replacement among drug molecules within a therapeutic category and the eleventh-most-common bioisosteric replacement overall. Sheridan, R., *The Most Common Chemical Replacements in Drug-Like Compounds*, 42 J. Chem. Inf. Comput. Sci. 103-108, 105-106 (2002) ("Sheridan") (DTX-210). By referring to such surveys, a POSA would have had a finite number of predictable bioisosteric replacements for phenyl that he or she could use to modify the lead compound. For these reasons, among others, Dr. Bannister will testify that a POSA would have been motivated to make this substitution without undue experimentation and with a reasonable chance of success of synthesizing a metabolically-stable SGLT2 inhibitor.

b. Substitution of the 4-chloro group with a 4-methyl group

Dapagliflozin has a 4-chloro group. Dr. Bannister will testify that a POSA would have known that chloro groups and methyl groups are bioisosteric and often used interchangeably. Patani at 3154 ("the chlorine atom is often viewed to be isosteric and isolipophilic with the methyl group"). Likewise, Sheridan taught that exchanging –Cl for –Me, or vice versa, was the most common bioisosteric substitution for molecules within a therapeutic category. Sheridan at 106. Moreover, the method of substituting a chloro group for a methyl group would have been

well known to a POSA. The '126 patent taught the synthesis of both methyl-substituted and chloro-substituted compounds. For these reasons, among others, Dr. Bannister will testify that a POSA would have been motivated to make this substitution without undue experimentation and with a reasonable chance of success of synthesizing a metabolically-stable SGLT2 inhibitor.

c. Substitution 4-ethoxy group for a 4-flurophenyl group

Dapagliflozin has a 4-ethoxy group. Dr. Bannister will testify that a POSA would have known (based on the '126 patent, the '117 patent, and U.S. Patent No. 7,129,220 ["the '220 patent"]) that 4-ethoxy groups and 4-phenyl groups are bioisosteric, specifically with respect to SGLT2 activity, and, therefore, that substituting one for the other would have little to no effect on the activity or selectivity of the resulting compound. Moreover, the method of substituting 4-ethoxy groups and 4-phenyl groups would have been known to a POSA. Indeed, the '220 patent taught the synthesis of both substituted compounds. In addition, a POSA would have known that the "substitution of hydrogen by fluorine is one of the more commonly employed monovalent isosteric replacements" (Patani at 3149) because it improves stability relative to non-fluorinated analogs. For these reasons, among others, Dr. Bannister will testify that a POSA would have been motivated to make this substitution without undue experimentation and with a reasonable chance of success of synthesizing a metabolically-stable SGLT2 inhibitor.

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In sum, a POSA would have had a "reasonable expectation" that making the foregoing bioisosteric modifications to dapagliflozin would successfully result in a metabolically-stable SGLT2 inhibitor because the prior art taught that these same modifications on structurally similar compounds maintained the anti-diabetic properties in the resulting compound. As Dr. Bannister will testify, making known bioisosteric replacements to a lead molecule, one *expects* to achieve high potency that is in line with the prior art lead; *expects* to circumvent

problematic issues that were solved by the prior art lead (*e.g.*, lower toxicity, increased bioavailability, increased stability, more favorable distribution, increased ease of formulation for administration to patients, etc.); and *expects* to achieve clinical efficacy, if the prior art lead is clinically efficacious. That is the point. And that is why bioisosteric changes, coupled with structural similarity, more than satisfy the "reasonable expectation" standard. *Imperial Chem. Indus.*, 777 F. Supp. at 370 (finding obviousness based on "bioisosteric replacement" and "structural similarity"); *see also In re Merck*, 800 F.2d at 1096 (in certain circumstances, "[s]tructural similarity, alone, may be sufficient to give rise to an expectation that compounds similar in structure will have similar properties").[7]

4. The Patents-in-Suit Are Obvious Over Example 10

For reasons closely parallel to those that render canagliflozin obvious over dapagliflozin, canagliflozin is similarly obvious over Example 10 of the '126 patent ("Example 10")—the precursor to dapagliflozin and the '117 patent. Dr. Bannister will testify that (i) a POSA would have selected Example 10 as a "natural choice" for a lead compound (*see supra* Section III.B.2.), (ii) the prior art provided motivation to implement minor modifications to improve on stability/efficacy/potency and evade competing patents (*see supra* Section III.B.3.), and (iii) a POSA would have had a reasonable expectation that making these modification would result in a metabolically-stable SGLT2 inhibitor with similar anti-diabetic properties (*see supra* Section III.B.3.) In fact, Canagliflozin is even more structurally similar to Example 10 than it is to dapagliflozin. It only takes two modifications to get from Example 10 to canagliflozin, both of which would have been obvious to a POSA: (i) substituting the distal phenyl ring with its

[7] Dr. Bannister's opinion is, therefore, not based on "hindsight." *In re Merck*, 800 F.2d at 1097 (using "*known bioisosteric replacement* provides sufficient basis for the required expectation of success, *without resort to hindsight*") (emphasis supplied).

bioisosteric replacement thiopene in a 2,5 orientation to maintain or improve efficacy (*cf. supra* Section III.B.3.a.); and (ii) substituting the 4-ethoxy group of the new thiopene ring to a 4-flurophenyl to minimize adverse effects and toxicity while maintaining improving efficacy (*cf. supra* Section III.B.3.c.).

5. The Differences Between Dapagliflozin/Example 10 And Canagliflozin Are Not "Sufficiently Great To Warrant A Patent"

Returning to first principles, the hypothetical posited by the Supreme Court in the seminal case *Graham* is the situation presented here: "[a]n invention which has been made, and which is new in the sense that the same thing has not been made before, may still not be patentable if the difference between the new thing and what was known before is not considered sufficiently great to warrant a patent." *Graham*, 383 U.S. at 14. Bioisosteric changes can be made and often are made—not for the purpose of discovering truly "novel" compounds—but for the purpose of creating a compound that is *not so different* that it loses the favorable biological activity, but *just different enough* (the pharmaceutical company hopes) to skirt a patent on the original compound. This is no secret. As reflected in contemporaneous publications, medicinal chemists often make bioisosteric replacements in a purposeful attempt to "circumvent a conflicting patent situation with potential competitors." Böhm, M. *et al*., *Development of New Hydrogen-Bond Descriptors and Their Application to Comparative Molecular Field Analyses*, J. 45 J. Med. Chem. 1585–97, 1585-86 (2002) (DTX-192).[8] Indeed, it is common knowledge that that is exactly what Mitsubishi did here:

[8] *See also* Lima at 48 (bioisosteric replacements are "useful in the molecular modification … including the design of *me-too* drugs, *i.e.* [a] therapeutic copy"); Nogrady, T. *et al*., *Basic Principles of Drug Design III, in Medicinal Chemistry: A Molecular and Biochemical Approach*, 106-82, 136 (Oxford Univ. Press, 3d. ed., 2005) ("Variations in ring structure are endless in drug synthesis, and are often used in the service of some other change or are introduced *simply for patent-right purposes*.") (emphasis supplied) (DTX-202); Bleicher, K. *et al., Lead Generation: Sowing the Seeds for Future Success*, 58 Chimia 588–600, 590 (2004) ("Navigating safely

> The [BMS] disclosures [in the '126 and '117 patents] coupled with the knowledge that [BMS] was actively evaluating SGLT2 inhibitors in the clinic did not go unnoticed. The focus of the discovery efforts of most [medicinal chemistry] groups subsequently shifted to C-aryl glucosides….
>
> In 2004, the first of many subsequent non-[BMS] C-aryl glucoside containing applications were published.[9] To obtain a proprietary position, these groups have used a variety of ***strategies to modify [dapagliflozin] in order to circumvent the constraints imposed by the [BMS] applications***. Some utilized substituents that were outside the BMS applications; some replaced one or both of the benzene rings with heteroaryls as an ***isosteric phenyl equivalent***,[10] and others modified the glucose moiety. In all instances, the spatial presentation inherent in ***the original pharmacophore has been maintained***: a planar central ring substituted 1,3 with a glucose-like moiety and a methano linked second planar ring.

Washburn, W., *Evolution of sodium glucose co-transporter 2 inhibitors as anti-diabetic agents*, 19(11) Expert. Opin. Ther. Patents 1485, 1488-89 (2009) ("Washburn") (DTX-213) (emphasis supplied). As the Supreme and the Federal Circuit have emphasized, there is no need to check "common sense" on the court house steps. *KSR*, 550 U.S. at 421; *Wyers*, 616 F.3d at 1238. Canagliflozin—based on purposefully nominal changes to the form of dapagliflozin, which were carefully calibrated to maintain the function of the original compound—is not the type of "invention" that U.S. patent laws are intended to protect. The difference between canagliflozin and dapagliflozin, in light of "what was known before," is simply not "sufficiently great to warrant a patent." *Graham*, 383 U.S. at 14.

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around large claims from existing patents or other publications can be a real challenge and needs a high level of *creativity* both from the chemistry and *from the patenting side*.") (emphasis supplied) (DTX-190).

[9] On July 30, 2004, Mitsubishi filed the application resulting in the issuance of the '788 patent.

[10] This is an apparent reference to the bioisosteric change that Mitsubishi made to dapagliflozin (*supra* Section III.B.3.a.) and/or Example 10 (*supra* Section III.B.4.b.).

C. Plaintiffs Cannot Rebut Zydus' Prima Facie Showing Of Obviousness

Once Zydus makes a *prima facie* case that canagliflozin is an obvious derivative of dapagliflozin in light of prior art, the burden will shift to Plaintiffs to rebut that case by offering objective indicia of nonobviousness, also known as secondary considerations. *Pfizer*, 480 F.3d at 1360 ("once a challenger has presented a prima facie case of invalidity, the patentee has the burden of going forward with rebuttal evidence").

1. Commercial Success

"Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). "Thus, the law deems evidence of (1) commercial success, and (2) some causal relation or 'nexus' between an invention and commercial success of a product embodying that invention, probative of whether an invention was non-obvious." *Id.* "If commercial success is due to an element in the prior art, no nexus exists." *Tokai*, 632 F.3d at 1369-70 (affirming holding that, "because [the patentee] failed to establish a nexus between the [claimed] feature and the alleged commercial success, [the patentee's] sales data were not pertinent to the court's obviousness determination").

As a threshold matter, a metabolically-stable SGLT2 inhibitor that lowers blood glucose levels when administered orally ***was*** "brought to market sooner" than Invokana®. *Merck*, 395 F.3d at 1376. Specifically, Farxiga® was first launched commercially in 2012 in Europe, whereas Invokana® was not launched commercially until 2013 in the United States. Thus, when Invokana® was approved for sale for the first time in 2013, Farxiga® was already a known, effective and commercially viable SGLT2 inhibitor. While it is true that Invokana® was launched in the U.S. before Farxiga®, the delay in launching Farxiga® in the U.S. is attributable

to the vagaries of the regulatory process. Specifically, the FDA changed the requirements for clinical trials of SGLT2 inhibitors after BMS's clinical trial for dapagliflozin was already underway. As a result, BMS had to start its clinical trial over, and Mitsubishi, in effect, jumped BMS in the regulatory queue. Thus, any early success that Invokana® had before Farxiga® was launched in the U.S. in no way suggests that Invokana® was nonobvious or (counter-factually) that Mitsubishi beat BMS to the SGLT2 metabolic-stability breakthrough. To the contrary, Invokana®'s early performance can be attributed to an artificial and short-lived monopoly on metabolically-stable SGLT2 inhibitors in the U.S., which is "weak" evidence at best of commercial success. *Merck*, 395 F.3d at 1377 ("Because market entry by others was precluded [by the FDA], the inference of non-obviousness of [the claimed invention], from evidence of commercial success, is weak.").

In any event, Invokana® was not commercially successful by any reasonable metric. Plaintiffs putative expert, Raymond S. Sims, M.B.A. ("Sims"), is expected to opine that the Invokana Products have been commercially successful based on "substantial sales," their supposed profitability, and their "market share" among SGLT2 inhibitors. Sims is further expected to opine that the alleged success of the Invokana Products is attributable to the "features and benefits of the products, and not marketing efforts, price, or any other economic factor." Zydus will, in turn, proffer DeForest McDuff, Ph.D. ("Dr. McDuff"), who is an expert in applied business economics with extensive experience in consulting, finance, and economic research. Dr. McDuff will opine that Sims' analysis of the commercial performance of the Invokana Products is fatally flawed because, among other reasons, Sims: (i) fails to adequately consider the impact of Invokana Products' severe health issues; (ii) provides a flawed analysis of

the Invokana Products' commercial performance; and (iii) provides a flawed analysis of nexus. Each of these issues will be previewed briefly here and presented in further detail at trial.

First, as Sims acknowledges, the FDA requires certain warnings on Invokana product labels, including, in particular, a so-called "black box" warning (about an increased risk of lower-leg amputations), which is the severest warning required by the FDA. The Invokana Products are the only SGLT2 drugs with a black box warning associated with amputations. Attempting to turn such an obvious liability on its head, Sims argues that the fact these products generated "substantial" sales despite these "challenges" is evidence of commercial success. As Dr. McDuff will opine, Sims is wrong. Internal Janssen documents indicate that the health and safety issues for the Invokana Products were significant and highly impactful. [redacted] Dr. McDuff will opine that, from an economic perspective, any sales, profits, or market share that occurred before the health and safety issues with the Invokana Products were widely known should be discounted. Instead, the commercial performance of the Invokana Products should account for its product profile as it is known today.

Second, Dr. McDuff will opine that Sims vastly overstates the performance of the Invokana Products because, among other things, he: (i) improperly focuses on Invokana

Products' gross sales; (ii) fails to account for the fact that the Invokana Products failed to meet internal expectations; (iii) improperly analyzes competition and calculates inflated market shares; (iv) fails to properly benchmark the Invokana Products' sales, profits, and market share, and (v) fails to adequately evaluate the Invokana Products' economic profitability or return on investment. In sum, Dr. McDuff will opine that Sims's economic analysis is fundamentally flawed and, therefore, significantly overstates the financial performance of the Invokana Products.

Third, Dr. McDuff will opine that Sims fails to show a nexus between the purported commercial success of the Invokana Products and the Patents-in-Suit. Specifically, Sims fails to adequately evaluate: (i) the claimed contributions of the Patents-in-Suit; (ii) each of the Invokana Products individually; (iii) price discounts and the impact on the Invokana Product sales; and (iv) marketing and promotional efforts and the impact on the Invokana Product sales. Most fundamentally, Sims fails to show how the Invokana Products' supposed success can be tied to anything particular about canagliflozin, as opposed to the generic fact that the active pharmaceutical ingredient in the Invokana Products is a metabolically-stable SGLT2 inhibitor that reduces blood glucose when administered orally—just like Farxiga® (dapagliflozin), Jardiance® (empagliflozin), and Steglatro® (ertugliflozin). "[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006) (commercial success has no probative value where "evidence clearly rebuts the presumption that [the claimed invention's] success was due to the claimed and novel features").

2. Unexpected Results

To be probative of non-obviousness, "evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the

difference would not have been expected by one of ordinary skill in the art at the time of the invention." *BMS*, 752 F.3d at 977. "Unexpected properties, however, do not necessarily guarantee that a new compound is nonobvious." *Id*. "While a 'marked superiority' in an expected property may be enough in some circumstances to render a compound patentable, a 'mere difference in degree' is insufficient." *Id*. (citations omitted). "And 'differences in degree' of a known and expected property are not as persuasive in rebutting obviousness as differences in 'kind'—*i.e*., a new property dissimilar to the known property." *Id*. (citations omitted). "When assessing unexpected properties, therefore, [courts] must evaluate the significance and 'kind' of expected results along with the unexpected results." *Id*. (citations omitted).

Here, the "closest prior art" (*BMS*, 752 F.3d at 977) is dapagliflozin.[11] There is nothing "unexpected" about the fact that canagliflozin, like dapagliflozin, is a metabolically-stable SGLT2 inhibitor. To the contrary, as discussed above in Section III.B.3., a POSA would expect bioisosteric changes to dapagliflozin to result in a metabolically-stable SGLT2 inhibitor with the same kind of biological activity. Similarly, there is no difference "in 'kind'—*i.e*., a new property dissimilar to the known property." *BMS*, 752 F.3d at 977. Zydus' expert Jonathan S. Williams, MD, MMSc ("Dr. Williams") will testify that all SGLT2 inhibitors—including canagliflozin and its predecessor dapagliflozin—have the same basic glycemic and non-glycemic benefits, which are known as "class effects." *Cf. In re Merck*, 800 F.2d at 1099 ("while there are some differences in degree between the properties of amitriptyline and imipramine, the compounds *expectedly* have the same type of biological activity" because the differences were "bioisosteric") (emphasis supplied).

[11] On February 4, 2003, the U.S. Patent and Trademark Office issued the '117 patent for dapagliflozin. *Eighteen months later*, on July 30, 2004, Mitsubishi filed the application that ultimately resulted in the issuance of the '788 patent for canagliflozin.

Nevertheless, one of Plaintiffs' experts, James R. Gavin III, M.D., Ph.D. ("Dr. Gavin")[12] claims that canagliflozin is "superior" to dapagliflozin at lowering blood glucose levels. However, as Dr. Williams will testify, there have been no published, peer-reviewed, head-to-head trials comparing the efficacy of canagliflozin and dapagliflozin. At most, any difference between the efficacy of canagliflozin and dapagliflozin is a "mere difference in degree," which is insufficient to rebut a *prima facie* showing of obviousness. *BMS*, 752 F.3d at 977; *see also In re Merck*, 800 F.2d at 1099 ("In the absence of evidence to show that the properties of the compounds differed in such an appreciable degree that the difference was really unexpected, we do not think that the Board erred in its determination that appellant's evidence was insufficient to rebut the prima facie case.").[13]

3. Skepticism

"General skepticism of those in the art" may be probative on nonobviousness. *Bristol-Myers Squibb*, 923 F. Supp. 2d at 679. Plaintiffs' expert, Dr. Gavin, asserts that SGLT2 inhibitors as a class were met with skepticism in the 2003-2004 time period. Two of Zydus' experts, Dr. Williams and Dr. Bannister, strongly disagree. Dr. Williams will testify that the developmental history of SGLT2 inhibitors was lengthy and well-established by the early 2000s. Far from being met with skepticism, the potential use of SGLT inhibitors as anti-diabetic agents had been consistently entertained by the medicinal chemistry community for decades—including by Mitsubishi's predecessor and, of course, BMS. *See supra* Section II.E. Moreover, a PubMed

[12] Zydus moved *in limine* to preclude Dr. Gavin's testimony as classic *ipse dixit*. D.I. Nos. 134 and 149. By discussing Dr. Gavin's opinions herein, Zydus does intend to waive its motion.

[13] Dr. Gavin also claims that the Invokana Products are superior as compared to the other two commercially-available SGLT-2 inhibitors, Jardiance (empagliflozin) and Steglatro (ertugliflozin), which were launched in 2014 and 2017 respectively. There is no solid support for that claim either. In any event, the material question is how canagliflozin compares to dapagliflozin, *i.e.*, the "closest prior art" (*BMS*, 752 F.3d at 977), not any subsequent art.

search of "SGLT" for the period 2002 to 2006 returns over sixty results in various areas of investigation.[14] Dr. Bannister concurs based on his own experience.

4. Long-felt But Unmet Need & The Failure Of Others

"Another objective indication of nonobviousness … is a long-felt but unmet need for the claimed invention." *Bristol-Myers Squibb*, 923 F. Supp. 2d at 682-83. "Long-felt need is closely related to the failure of others. Evidence is particularly probative of obviousness when it demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *Id*. (citation omitted). The Federal Circuit has held and reiterated that a "court is to assess whether a long-felt and unmet need existed as of the 'filing date of the challenged invention,' not as of 'the time the invention becomes available on the market, when it can actually satisfy that need.'" *Id*. (quoting *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009)).

Here, the earliest "filing date of the challenged invention" is July 30, 2004 (the '788 patent). There is no dispute that, historically, there was a "long-felt unmet need" for a metabolically-stable SGLT2 inhibitor. The operative question is, therefore, whether that "unmet need existed" as of July 30, 2004. *Bristol-Myers Squibb*, 923 F. Supp. 2d at 683. The answer is a "no." The '117 patent for dapagliflozin—*i.e.*, a metabolically-stable SGLT2 inhibitor—was published on February 4, 2003 (eighteen months before July 30, 2004). In short, there was no "long-felt but ***unmet*** need." The failure-of-others secondary consideration does not militate in favor of nonobviousness for the same reason. Many others may have failed to develop a

[14] PubMed is maintained by the U.S. National Library of Medicine of the National Institutes of Health. https://pubmed.ncbi.nlm.nih.gov/

metabolically-stable SGLT2 inhibitor. But at least BMS succeeded before Mitsubishi did, as Mitsubishi's medicinal chemists were acutely aware.

5. Praise and Industry Recognition

Industry praise and recognition are sometimes considered as an indication of nonobviousness. Here, Dr. Gavin asserts that Invokana® received industry recognition and praise in the United States. However, Dr. Gavin does not even contend that any such industry praise or recognition was tied to any difference between the chemical structure or efficacy of canagliflozin and dapagliflozin. In any event, any praise of Invokana® proved to be premature and short-lived. The FDA's black-box warnings have effectively muzzled any such praise.

IV. THE '788 PATENT IS INVALID FOR DOUBLE PATENTING[15]

A. The Obviousness-Type Double Patenting Doctrine Applies

"Non-statutory, or obviousness-type, double patenting is a judicially created doctrine designed to foreclose claims in separate applications or patents that do not recite the 'same' invention, but nonetheless claim inventions so alike that granting both exclusive rights would effectively extend the life of patent protection." *Takeda Pharm. Co. v. Doll*, 561 F.3d 1372, 1375 (Fed. Cir. 2009) (citation and quotations omitted). In other words, the obviousness-type double patenting doctrine "prevents an applicant from extending patent protection for an invention beyond the statutory term by claiming a slight variant" of the same invention in a separate patent. *Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1378 (Fed. Cir. 2003) (patentees are limited to "one patent term per invention or improvement").

"In general, the obviousness analysis applies to double patenting, except for three distinctions." *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 999 (Fed. Cir.

[15] Defendant Aurobindo Pharma USA Inc. joins in the arguments set forth in this section.

2009) (citing *Geneva Pharm*, *supra*). "First, statutory obviousness compares claimed subject matter to the prior art, while non-statutory double patenting compares claims in an earlier patent to claims in a later patent or application." "Second, double patenting does not require inquiry into a motivation to modify the prior art." *Id.*, 566 F.3d at 999. "Finally, double patenting does not require inquiry into objective criteria suggesting non-obviousness." *Id*.

An obviousness-type double patenting analysis boils down to the question whether the claims in two separate patents issued to the same inventor are patentably distinct or obvious variants of each other. As applied here, the question is whether the method of treatment claims in the '788 Patent (claims 12 and 20) are patentably distinct from the method of treatment claims in the '219 Patent (claim 22). As Dr. Bannister has opined and will testify at trial, the answer is no. The claims each describe, in sum and substance, the oral administration of canagliflozin as a treatment for diabetes. *Cf.* DTX-1 at 69973 with DTX-2 at 70089.

But the question remains which of the two patents—the '788 Patent or the '219 Patent—is invalid. Here, the '788 Patent was issued first but expires after the '219 Patent.[16] Does the earlier-filed patent (the '788 patent) invalidate the later-filed patent (the '219 Patent)? Or does the earlier-expiring patent (the '219 Patent) invalidate the later-expiring patent (the '788 patent)? The Federal Circuit addressed this precise issue in *Gilead Scis., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208 (Fed. Cir. 2014). The *Gilead* case, like this case, involved a "later-issued but earlier-expiring patent." *Id.* at 1211. The patentee argued that the issuance date controls and that the earlier-issued patent should invalidate that later-issued patent. The Federal Circuit rejected that argument, reasoning that, "if the double patenting inquiry was limited by issuance date,"

[16] Specifically, the '788 patent was issued on March 17, 2011 and expires on July 14, 2027, whereas the '219 Patent was issued July 17, 2012 and expires on April 11, 2025.

inventors could game the system to "obtain additional patent term exclusivity for obvious variants of their inventions while also exploring the value of an earlier priority date during prosecution. *Gilead*, 753 F.3d at 1215. The Federal Circuit, therefore, held that, "looking instead to the earliest expiration date of all the patents an inventor has on his invention and its obvious variants best fits and serves the purpose of the doctrine of double patenting." *Id*. at 1216; *see also Novartis Pharm. Corp. v. Breckenridge Pharm. Inc*., 909 F.3d 1355, 1362-63 (Fed. Cir. 2018) (reiterating principle that "proper reference point for an obviousness-type double patenting inquiry is the expiration date of the patent in question").[17] Accordingly, under *Gilead* and *Breckenridge*, the method of use claims in the '219 patent (the later-issuing, earlier-expiring patent) invalidate the method of use claims in the '788 patent (the earlier-issuing, later-expiring patent). As a result, the patent term for the method of use claims in both patents expires on April 11, 2025—*i.e*., the "earliest expiration date." *Gilead*, 753 F.3d at 1216.

B. The Safe Harbor Is Unavailable

Plaintiffs contend that the safe-harbor provision of 35 U.S.C. § 121 shields the '788 patent from invalidity for obviousness-type double patenting in view of the '219 patent. The safe-harbor "protects a patent that issues on a divisional application from invalidation based on a related patent that issued on an application as to which a restriction requirement was made, or on an application filed as a result of such a requirement." *G.D. Searle LLC v. Lupin Pharm., Inc.*,

[17] In a companion case, *Novartis AG v. Ezra Ventures LLC*, 909 F.3d 1367 (Fed. Cir. 2018), the Federal Circuit held that "obviousness-type double patenting does not invalidate an otherwise validly obtained PTE [patent term extension] under § 156." *Id*. at 1369. However, *Ezra* dealt exclusively with the "interplay between a patent term extension (PTE) granted pursuant to 35 USC § 156 and the obviousness-type double patenting doctrine." *Id*. Here, the '788 patent was extended by a patent term amendment ("PTA") under 35 USC § 154, not a PTE. The Federal Circuit expressly distinguished a PTE and a PTA in the context of obviousness-type double patenting. *Ezra*, 909 F.3d at 1374 (§ 154 "expressly excludes patents in which a terminal disclaimer was filed," but § 156 contains "no similar provision").

790 F.3d 1349, 1352 (Fed. Cir. 2015). The Federal Circuit applies "a strict test for application of section 121, given the potential windfall a patent term extension could provide to a patentee." *Id.* at 1354 (citation, quotations and alterations omitted). Among other stringent requirements, a party invoking the § 121 safe harbor must show that both the challenged patent and the reference patent were filed "as a result of" a restriction requirement. *Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1352 (Fed. Cir. 2010); *see also* Manual of Patent Examining Procedure, Eight Edition, Revision 6 (Sept. 2007) § 804.01 at 800-30 (safe-harbor "does not apply where the divisional application was voluntarily filed by the applicant and not in response to an Office requirement for restriction") (DTX-342).

As applied here, Plaintiffs are only entitled to invoke the safe-harbor against using the '219 patent "as a reference" against the '788 patent if, among other requirements, both underlying applications were filed "as a result of" a restriction requirement. The answer "depends on an interpretation of the prosecution history." *G.D. Searle*, 790 F.3d at 1351. James T. Carmichael ("Carmichael"), who is an expert on practices and procedures before the United States Patent and Trademark Office (the "PTO"), will testify at trial, among other things, that the '219 patent application was not filed "as a result of" any restriction requirement imposed on the '788 Patent. To the contrary, the applicant affirmatively and voluntarily "cancelled" the method of treatment claims in the '788 Patent "in order to expedite prosecution" (DTX-33 at 15-16) and took several other procedurally voluntary acts, each of which independently vitiates the availability of the safe harbor. The applicant chose to do so, even though the PTO informed the applicant that the original "restriction requirement … [had been] withdrawn" and repeatedly warned the applicant that, "[o]nce the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable" (DTX-45 at 3; *see also* DTX-43 at 2-3; DTX-32 at 20).

Accordingly, for these reasons, among others, Plaintiffs are not entitled to invoke the safe-harbor.

CONCLUSION

For the reasons set forth herein, as well as reasons to be established at trial, the asserted claims of the ’788 patent, the ’403 patent, and the ’219 patent should be declared invalid as obvious, and the ’788 patent should be declared invalid for the independent and alternative reason that it violates the obviousness-type double patenting doctrine.

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Respectfully submitted,

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